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Decision Analysis of the Benefits and Costs of Screening for Prostate Cancer

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13. SUPPLEMENTARY NOTES

14. ABSTRACT (adapted from Hayes et al, Annals of Internal Medicine, June 2013[1])
PURPOSE/SCOPE: Observation has emerged as a strategy to avoid overtreatment in men with screen-detected low-risk prostate cancer (CaP). This analysis examines the cost-effectiveness of observation with watchful waiting (WW) as experienced in the PIVOT study or active surveillance (AS), radical prostatectomy (RP), radiation therapy (IMRT), and brachytherapy (BT) in these men. METHODS: A Markov Monte Carlo model was constructed. Main outcomes were costs (2012US$) and quality-adjusted life-years (QALYs) for men aged 65 and 75 years. RESULTS: Observation was more effective and less costly than initial treatment. Compared with AS, WW provided 2 additional months of QALE (9.02 vs. 8.85 y) at a savings of $15374 ($24520 vs. $39894) in men aged 65 and 6.14 vs. 5.98y at a savings of $11746 ($18302 vs. $30048) in men aged 75. BT was the most effective and least expensive initial treatment. Treatment became more effective than observation when it led to greater reductions in CaP death (hazard ratio, 0.47 vs. WW; 0.64 vs. AS). AS became as effective as WW in men aged 65 when the probability of progressing to treatment on AS decreased below 63% or when the quality of life with AS versus WW was 4% higher in men aged 65. WW remained least expensive in all analyses.
CONCLUSIONS: In this model, observation with WW and AS is a cost-effective alternative to initial treatment in men 65 and 75 years of age.

15. SUBJECT TERMS
Prostate cancer, screening, cost-effectiveness analysis

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INTRODUCTION

This final report details the achievements made as a result of the Physician Research Training Award entitled "Decision analysis of the benefits and costs of screening for prostate cancer". The goal of the proposed research was to develop a decision analytic model of PSA screening for prostate cancer in order to permit the analysis of the effect of various PSA screening strategies on life expectancy (LE), quality-adjusted LE (QALE), and the cost-effectiveness of screening. The comparator was to be a natural history model of unscreened, conservatively-treated prostate cancer based on primary data. It was hypothesized that the optimal screening strateg(ies) for prostate cancer would be dependent not only upon mortality benefit, but also upon the value patients place on health states and costs.

This report will summarize the progress made on the tasks outlined in the Statement of Work. Due to difficulties that arose in conducting Task 1, the majority of the work conducted was on Task 3. The model developed to accomplish the goals described in Task 3 compared first the effectiveness, then the cost-effectiveness of treatment strategies for low-risk, clinically localized prostate cancer. In the initial iteration of this model, the strategies studied included active surveillance, radical prostatectomy, brachytherapy, intensity-modulated radiation therapy, and proton beam therapy. It was found that active surveillance is the most effective strategy of these, or associated with the greatest quality-adjusted life expectancy, but brachytherapy is the least expensive treatment. Active surveillance remained cost-effective under all scenarios constructed in men 65 years of age. Results of this model were published in the *Journal of the American Medical Association*[2], presented at annual meetings of professional societies, discussed in a teleconference sponsored by the Institute for Healthcare Improvement and *JAMA*, and discussed at the Cancer Intervention and Surveillance Modeling Network's (CISNET) Annual Conference at the National Institutes of Health. A second manuscript, incorporating data published in 2012 from the PIVOT trial[3], compares the cost-effectiveness of watchful waiting to active surveillance, brachytherapy, IMRT, and radical prostatectomy was published in *Annals of Internal Medicine*[1].

I am very grateful to the Department of Defense for providing the funding to make this work possible.

KEYWORDS

Prostate cancer, screening, PSA, cost-effectiveness analysis, active surveillance, watchful waiting, quality of life, decision analysis

OVERALL PROJECT SUMMARY

TASK 1: Develop a Markov Monte Carlo disease model of the natural history of prostate cancer.

Methods. We will create a Markov Monte Carlo disease model of the natural history of prostate cancer. Individuals will progress from a disease-free state to preclinical disease to clinically-detectable prostate cancer; each individual will have a PSA value and, in those with prostate cancer, a Gleason score. Men with disease will progress from clinically localized to regional to metastatic disease and death of prostate cancer; they may also progress between Gleason scores. Death of other causes can occur from any health state.

Task 1.1 Utilizing data from the published literature, create a model of the preclinical development of prostate cancer. Estimates of age-specific prevalence of preclinical prostate cancer, correlation of the presence of preclinical disease with serum PSA, and evaluation of PSA rise in the serum of patients subsequently diagnosed with prostate cancer will be obtained from the published literature. This data will be combined using regression analysis to estimate the preclinical incidence and progression of disease based on Gleason score and PSA.

Task 1.2 Utilizing data from the control arm of the ERSPC, create a model of the characteristics of prostate cancer at diagnosis in a contemporary, unscreened population. We will utilize data provided by investigators from the ERSPC to model tumor and patient characteristics of clinically-diagnosed prostate cancer in the modern era, including age, stage at diagnosis, and Gleason score,

Task 1.3 Utilizing data from a database of men diagnosed in the pre-PSA era, create a model of the progression of clinically localized, conservatively-treated prostate cancer. We have created a database of such men in collaboration with investigators from Örebro, Sweden, that will be used to develop transition probabilities between model health states described in Task 1.1. We will collaborate with Dr. D'Amico in interpretation and analysis of the data, particularly with regard to modeling PSA kinetics.

Task 1.4 Calibrate the model using data from published studies of the natural history of conservatively-treated prostate cancer and recent clinical trials. We will calibrate the model to reproduce target outputs within 5% of pre-selected values. Sources of calibration data for our model will include incidence data from the control arm of the ERSPC and the published literature.

Timeline: The collection and analysis of data from the ERSPC and the Örebro cohort and from the published literature will take 9 months. Construction and calibration of the natural history model will take 15 months. Two manuscripts will be generated: the first will reflect findings from the primary data, and the second will describe the natural history model. I will also take a course during the fall of the first year in order to acquire skills necessary to develop transition probabilities from the published literature.

Outcomes: This task will result in the creation of a natural history model of unscreened, conservatively-treated prostate cancer that will provide data on characteristics of patients at clinical diagnosis and at progression, rates of progression, and prostate cancer specific- and all-cause mortality.

Final report:

An important feature of this model as originally designed was that it was to have been able to trace the natural history of prostate cancer in men diagnosed in the pre-PSA era whose prostate cancer had been regraded in the modern era, hence avoiding the concern raised by the fact that Gleason scores have shifted higher over the past 20 years. The construction of this portion of the model was therefore crucially dependent upon data obtained from the Örebro cohort, as outlined in Task 1.3. However, as described in previous progress reports, during analysis of the data from Örebro, I realized that in our cohort, Gleason score did not correlate with prostate cancer-specific survival. This finding is at odds with the published literature and prompted me to question the accuracy of the Gleason grading performed. A representative selection of pathologic samples was obtained from Örebro and regraded by a pathologist at Massachusetts General Hospital. It was realized that serious errors in Gleason scoring had been made and that as a result, this data was unusable.

Unfortunately, despite considerable effort extending through the third year of this grant, it was impossible to obtain the original pathology samples from the Örebro cohort for regarding in a timely manner, as the samples had been dispersed to several countries for other research endeavors. I therefore turned to other possible sources of long term outcomes data on men who were diagnosed with prostate cancer in the pre-PSA era. The most promising source of data was the SPCG-4 trial, a randomized controlled trial initiated in 1989 that compared watchful waiting to radical prostatectomy in men diagnosed in Sweden in the pre-PSA era[4]. However, after a delay in response of almost a year, my request for this data was denied. As funding for this project was coming to an end, I elected to continue to concentrate on constructing the model described in Task 3.

TASK 2: Compare the clinical effectiveness, cost and cost-effectiveness of PSA screening strategies.

Methods. ***Task 2.1 Vary the biopsy threshold for screening PSA, the interval between screening events, and establish the effect of PSA kinetics prior to diagnosis on screening strategies.*** We will first assess the effect of annual screening varying PSA biopsy thresholds. We will then vary the interval between PSA screening events using these thresholds. These two variables will then be modified simultaneously to identify the screening strategy that maximizes LE. Subsequent analyses will focus on identifying the optimal screening strategy once a PSA velocity has been established. The model will vary PSA velocity, biopsy threshold, and subsequent screening interval simultaneously. Similar analyses will be performed using PSA doubling time.

Task 2.2 For each strategy, establish the lead time and effect on prostate cancer incidence. To quantitate lead time, the difference in time between screen diagnosis and clinical diagnosis of prostate cancer will be calculated. To estimate incidence and overdiagnosis rates, incidence in the presence and absence of screening will be compared.

Task 2.3 Extend the model to include quality of life adjustments (utilities) and costs and use the model to estimate the clinical effectiveness, cost, and cost-effectiveness of each screening strategy.

We will run the model using both community and patient-elicited utilities from the published literature and unpublished results provided by Dr. Susan Stewart. Dr. Swan will assist in analysis of these utilities and their incorporation into the model. Costs will be estimated from a societal perspective. Costs and QALYs will be discounted. Total cost will be the sum of direct medical costs. Costs will be calculated using data from the medical literature or local institutional cost data and will be expressed in 2012 dollars.

The model will estimate the QALE and costs associated with each screening strategy. The model results will estimate the magnitude of benefit for intermediate and long-term outcomes, costs of care, and incremental cost-effectiveness.

Task 2.4 Identify model parameters likely to cause a shift in model results using sensitivity analysis. We will perform sensitivity analysis on parameters likely to have a significant effect on LE in our model. The model will be run across a literature-derived plausible range of probabilities for selected variables.

Timeline: Modification of the model to assess screening strategies, model calibration, and the calculation of lead time, incidence, and overdiagnosis rates will take approximately one year. Identification of costs, analysis and incorporation of utilities, cost-utility analysis and sensitivity analysis are projected to take nine months. I will take several courses at HSPH during the first two years to acquire the skills necessary for this task. One manuscript will be generated after completion of the screening model to describe the effect of screening on LE in conservatively-treated patients and the lead time and overdiagnosis associated with screening; the second at the completion of the CEA.

Outcomes: This task entails the creation of a PSA screening model that will compare outcomes in screened versus unscreened conservatively-treated men. Outcomes will include LE, QALE, and cost-effectiveness for each strategy and identification of the strategy that maximizes each of these outcomes; secondary outcomes will include lead time, incidence, and overdiagnosis rates for each strategy.

Final report:

It was not possible to complete Task 2 given its dependence on Task 1. However, a model incorporating prostate cancer treatment practices was constructed and is described as part of Task 3 below.

TASK 3: Modify the model created in Task 2 to include modern treatment practices to evaluate the clinical effectiveness, cost, and cost-effectiveness of the PSA screening strategies described above.
Methods. ***Task 3.1 Extend the model created in Task 2 to include modern treatment practices.*** We will incorporate modern treatment practices into the model to determine the effect of screening and treatment of screen-diagnosed disease on LE, QALE, and its cost-effectiveness. Treatments and outcomes will be obtained from the published literature and expert opinion, and sensitivity analysis will be performed.
Task 3.2 Extend the model to include quality of life adjustments (utilities) and costs and use the model to estimate the effectiveness, cost, and cost-effectiveness of each screening strategy. In treated men, utilities and costs will be calculated, and effectiveness and cost-effectiveness of each screening strategy will be estimated, as described in Task 2.3.
Task 3.3 Explore the role of future, as-yet-undeveloped diagnostic tests in screening for prostate cancer to establish the test characteristics required in order to identify men with clinically significant disease. The creation of a natural history model will enable us to identify the characteristics of prostate cancer most predictive of outcomes. Decision analytic modeling will highlight predictors of adverse outcomes in our model and will enable us to use them to characterize an "ideal" screening test.
Timeline: Modification of the model to include modern treatment practices and its calibration will take one year. Identification of costs, analysis and incorporation of utilities, cost-utility analysis and sensitivity analysis are projected to take nine months; analysis and comparison of these results with those obtained in Task 2 will take 3 months. Two manuscripts will be produced: the first describing the effect of screening on LE in treated vs. untreated men, the second at the completion of the CEA. Courses I will take to acquire skills necessary for this task will be taken during the second and third years. I will attend seminars and national meetings and continue clinical work with prostate cancer patients throughout the award period.
Outcomes: Outcomes for this task will include LE, QALE, and cost-effectiveness for each screening strategy in men treated for prostate cancer and identification of the screening strategy that maximizes each of these outcomes.

Final report:
A Markov Monte Carlo model was created comparing a strategy of active surveillance to treatment at diagnosis with radical prostatectomy or radiation therapy using brachytherapy, intensity-modulated radiation therapy, or proton beam therapy. A societal perspective was taken with a lifetime horizon. A systematic review of the literature was performed to establish transition probabilities for disease outcomes and for the probabilities of incurring complications of surgery and side effects (erectile dysfunction, urinary incontinence, gastrointestinal dysfunction)[5-7]. Utilities, or patient preferences, were obtained from literature review and from personal communication[8-10], (personal communication, Stewart). Costs were obtained from Medicare reimbursement schedules and included costs of initial treatment, treatment of side effects, and patient time costs. Sensitivity analyses were performed on key parameters. Outcomes included QALE, costs, and cost-effectiveness. Life expectancy was assumed to be equal for all approaches in these men with low-risk disease in the base case, and this assumption was varied in sensitivity analysis.

The results of this model were presented at ASCO's Genitourinary Cancers Symposium in March 2010 and at a moderated poster session at the ASCO Annual Meeting in June 2010.

The manuscript of the comparative effectiveness of active surveillance as compared to initial treatment without costs in 65 year old men was published in JAMA in December 2010 (please see Appendix)[2]. In this study, the QALE benefit of AS was examined in detail. On multiple sensitivity analyses, it was found that the QALE advantage of AS is quite robust: it remained the preferred strategy over initial treatment even if the risk of progressive disease or prostate cancer-specific death on AS was almost doubled, or the risk of side effects of treatment was halved. However, utilities played a key role in establishing the QALE advantage of AS. In particular, the value placed by individuals on being on AS and on having been treated was a major determinant of whether AS was favored. This analysis determined the utility thresholds at which initial treatment would be favored over AS.

Subsequently, the cost-effectiveness model was extensively revised and expanded, in particular the cost structure, modifying it to include more detail regarding costs incurred on active surveillance and to reflect one-time vs. recurrent costs, among other alterations. We also expanded the model to include men ages from 55-75. A portion of these results were presented in an oral presentation session at the Society for Medical Decision Making's annual conference in Toronto in October 2010.

We submitted a manuscript of our cost-effectiveness analysis to *Annals of Internal Medicine* and after extensive revision and expanding the manuscript to incorporate a watchful waiting strategy based on the results of the PIVOT study comparing watchful waiting to radical prostatectomy in a screened population[3], this manuscript was published in June 2013[1] (please see Appendix). This analysis compares the cost-effectiveness of watchful waiting, active surveillance, brachytherapy, intensity-modulated radiation therapy, and radical prostatectomy.

In this study[1], we found that watchful waiting is both more effective and less expensive than either active surveillance or initial treatment. Compared with active surveillance, watchful waiting provided 2 additional months of QALE (9.02 vs. 8.85 years) at a cost savings of $15 374 ($24 520 vs. $39 894) in men aged 65 years and 2 additional months (6.14 vs. 5.98 years) at a savings of $11 746 ($18 302 vs. $30 048) in men aged 75 years. Brachytherapy was the most effective and least expensive initial treatment. Treatment became more effective than observation when it led to more dramatic reductions in prostate cancer death (hazard ratio, 0.47 vs. watchful waiting and 0.64 vs. active surveillance). Active surveillance became as effective as watchful waiting in men aged 65 years when the probability of progressing to treatment on active surveillance decreased below 63% or when the quality of life with active surveillance versus watchful waiting was 4% higher in men aged 65 years or 1% higher in men aged 75 years. Watchful waiting remained least expensive in all analyses.

The model described above is specific to men with low-risk prostate cancer (Gleason $\leq$ 3+3; clinical stage $\leq$T2a, PSA <10 ng/mL). Modifications necessary to generalize this model to all men treated after screening include establishing prostate cancer-specific outcomes for men with intermediate and high-risk disease, outcomes that are expected to be reflected in shorter life expectancies for men with higher-risk disease. Expanding the model to include men with intermediate and high-risk prostate cancer was the primary focus during the final year of this award.

The source of data for this portion of Task 3 is very exciting. A project that evolved out of this model is a cost-effectiveness analysis that will assess whether intermediate clinical endpoints exist that can replace overall survival for the approval of adjuvant therapies for clinically localized prostate cancer. As part of a larger international collaboration, a database is currently being assembled at DFCI combining primary data on patients and outcomes for over 45,000 men with primarily intermediate- and high-risk, clinically localized prostate cancer who underwent treatment for their disease as part of a clinical trial. Access to this data will enrich the model immeasurably, as we will be able to develop probabilities directly from the primary data as opposed to extrapolating from published results of multiple different trials with varying endpoints. The structure of the model of intermediate and high-risk prostate cancer has been completed and testing is ongoing, but probabilities are not yet available from this database for use in the model to generate results as the data continues to be assembled and processed by the statisticians. It is anticipated that probabilities will be available for use in this model later this year. Funding from the Prostate Cancer Foundation was obtained to support the modeling component of this larger effort starting July 2014.

Completed abstracts and manuscripts are listed in the Publications section of this report.

KEY RESEARCH ACCOMPLISHMENTS

In summary, work completed on this grant proposal has demonstrated that

a) in screen-detected men with low-risk prostate cancer, active surveillance is a cost-effective alternative to initial treatment with radical prostatectomy or radiation therapy (with brachytherapy, intensity-modulated radiation therapy, or proton beam therapy), for men between 55 and 75 years of age at diagnosis.
b) the quality-adjusted life expectancy benefit of active surveillance seen in these men is robust but depends upon the patient preferences, or utilities, associated with being on active surveillance and with having been treated.
c) observation with watchful waiting as practiced in the PIVOT study is associated with improved QALE and is cost saving compared to either active surveillance or initial treatment in men 65 and 75 years of age.

CONCLUSIONS

In screen-detected men with low-risk prostate cancer, observation is a safe and effective alternative to initial treatment. In our model comparing active surveillance (AS) to initial treatment, the quality of life advantage associated with AS is robust, reflecting the deferred and substantially lower incidence of side effects of treatment experienced by men on AS. AS is associated with significant improvements in QALE even in analyses in which the probability of dying of prostate cancer or of developing progressive disease on AS is increased. However, our finding that the optimal strategy is sensitive to utility weights is evidence that the decision whether to pursue AS must be individualized. In future, models incorporating individual patient utilities may be available to assist patients and their caregivers to estimate the risks and potential benefits of AS prior to making this decision.

In particular after the publication of the PIVOT trial demonstrated no survival benefit to radical prostatectomy in men with low-risk prostate cancer, watchful waiting has gained attention as an intriguing alternative both to initial treatment and to the more interventionist active surveillance. When we modeled the results of the PIVOT study, it was found that watchful waiting was both more effective and less expensive than either active surveillance or initial treatment, even if the risk of dying of prostate cancer on active surveillance is half that of watchful waiting. Again, however, patient preferences were central to the quality of life advantage seen with observation.

Observation for low-risk prostate cancer is a promising strategy both on an individual and on a societal level, and increasingly media and professional attention is making it a more recognized alternative to initial treatment. However, the optimal approach for surveillance is not yet known – how little intervention is both safe and acceptable to patients and health care providers has yet to be determined. Our model was the first to quantitate the quality of life advantages of observation over initial treatment in men with low-risk prostate cancer in an exhaustive manner. Future directions for this model would include creating an individualized version of the model that men newly-diagnosed with prostate cancer could use, entering their own preferences to determine the best treatment strategy for them. In addition, the model is part of an effort to identify intermediate clinical endpoints that may replace overall survival in order to facilitate earlier approval of novel adjuvant therapies for clinically localized disease.

PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS

Peer-Reviewed Scientific Journals:

Hayes JH, Ollendorf DA, Pearson SD, Barry MJ, Kantoff PW, Stewart ST, Bhatnagar V, Sweeney CJ, Stahl JE, McMahon PM. Active surveillance compared with initial treatment for men with low-risk prostate cancer: a decision analysis. JAMA. 2010;304(21):2373-80. *(accompanied by an editorial: Thompson IM, Klotz L. Active Surveillance for Prostate Cancer. JAMA 2010;304(21):2411-12.)*

Hayes JH, Ollendorf DA, Pearson SD, Barry MJ, Kantoff PW, Lee PA, McMahon PM. Observation vs. initial treatment for men with localized low-risk prostate cancer: A Cost Effectiveness Analysis. Ann Intern Med. 2013;158:853-860

Hayes JH, Barry MJ, McMahon PM. Observation versus initial treatment for prostate cancer. Ann Intern Med. 2013; Oct 15;159(8):574

Invited Articles:

Hayes JH, Barry MJ. Commentary on screening for prostate cancer using prostate-specific antigen: current status and future directions. Oncology 2011. May; 25(6): 468-478.

Hayes JH, Barry MJ. Screening for Prostate Cancer With the Prostate-Specific Antigen Test: A Review of Current Evidence. JAMA. 2014;311(11):1143-1149.

Abstracts:

Hayes JH, Ollendorf DA, Pearson SD, McMahon PM. Cost-effectiveness analysis of therapeutic options for low-risk prostate cancer. ASCO Genitourinary Cancers Symposium. 2010; abstr 170.

Hayes JH, Ollendorf DA, Barry MJ, Pearson SD, McMahon PM. Therapeutic options for low-risk prostate cancer: A cost-effectiveness analysis. J Clin Oncol 28:7s, 2010 (suppl; abstr 6012).

Hayes JH, Ollendorf DA, Barry MJ, Pearson SD, McMahon PM. A Cost-effectiveness analysis of therapeutic options for low-risk prostate cancer. Med Decis Making, January/February 2011; vol. 31, 1: p.E100.

INVENTIONS, PATENTS, AND LICENSES

Nothing to report.

REPORTABLE OUTCOMES

A Markov Monte Carlo simulation model of low-risk, clinically localized prostate cancer analyzing the quality of life and cost of treatment vs. observation has been created. This model is available to the public as a tool for further analysis and modification to address questions surrounding the treatment of low-risk disease.

OTHER ACHIEVEMENTS

Funding applied for based on work supported by this award

Prostate Cancer Foundation Young Investigators Award.
Applied for and received, grant period July 2010 to July 2013.
The funds from this award are used to pay the salary of a computer programmer who is assisting in the development of the natural history model.

NIH/NCI R01CA183958-01. "Opening the Black Box of Cancer Policy Models".
Co-PI. Funding requested for 2014-2017. Applied June 2013; not funded.
Utilizing existing models of cancer, this project will develop a software platform that will address modeling's black box reputation and allowpolicymakers to interact more fully with the model predictions, capabilities and limitations.

Prostate Cancer Foundation Award.
"Implementing an Intermediate Clinical Endpoint for Clinical Trials of Adjuvant Therapy for Prostate Cancer: A Decision Analysis"
Applied for and received, grant period July 2014 through December 2015.

Employment or research opportunities applied for and/or received based on experience/training supported by this grant

Promotion to Assistant Professor, October 2013.

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APPENDICES

ORIGINAL CONTRIBUTION

Active Surveillance Compared With Initial Treatment for Men With Low-Risk Prostate Cancer

A Decision Analysis

Julia H. Hayes, MD
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Michael J. Barry, MD
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Context In the United States, 192 000 men were diagnosed as having prostate cancer in 2009, the majority with low-risk, clinically localized disease. Treatment of these cancers is associated with substantial morbidity. Active surveillance is an alternative to initial treatment, but long-term outcomes and effect on quality of life have not been well characterized.

Objective To examine the quality-of-life benefits and risks of active surveillance compared with initial treatment for men with low-risk, clinically localized prostate cancer.

Design and Setting Decision analysis using a simulation model was performed: men were treated at diagnosis with brachytherapy, intensity-modulated radiation therapy (IMRT), or radical prostatectomy or followed up by active surveillance (a strategy of close monitoring of newly diagnosed patients with serial prostate-specific antigen measurements, digital rectal examinations, and biopsies, with treatment at disease progression or patient choice). Probabilities and utilities were derived from previous studies and literature review. In the base case, the relative risk of prostate cancer–specific death for initial treatment vs active surveillance was assumed to be 0.83. Men incurred short- and long-term adverse effects of treatment.

Patients Hypothetical cohorts of 65-year-old men newly diagnosed as having clinically localized, low-risk prostate cancer (prostate-specific antigen level <10 ng/mL, stage ≤T2a disease, and Gleason score ≤6).

Main Outcome Measure Quality-adjusted life expectancy (QALE).

Results Active surveillance was associated with the greatest QALE (11.02 quality-adjusted life-years [QALYs]), followed by brachytherapy (10.5 QALYs), IMRT (10.43 QALYs), and radical prostatectomy (10.23 QALYs). Active surveillance remained associated with the highest QALE even if the relative risk of prostate cancer–specific death for initial treatment vs active surveillance was as low as 0.6. However, the QALE gains and the optimal strategy were highly dependent on individual preferences for living under active surveillance and for having been treated.

Conclusions Under a wide range of assumptions, for a 65-year-old man, active surveillance is a reasonable approach to low-risk prostate cancer based on QALE compared with initial treatment. However, individual preferences play a central role in the decision whether to treat or to pursue active surveillance.

JAMA. 2010;304(21):2373-2380 www.jama.com

In 2009, 192 000 men were diagnosed as having prostate cancer in the United States. Of these men, 70% will have been classified as having low-risk, clinically localized disease, and more than 90% will have undergone initial treatment.[1-4] Initial treatment choices include surgical resection or radiation therapy. The majority of men experience at least 1 adverse effect of treatment.[5-7]

In the era of prostate-specific antigen (PSA) screening, up to 60% of men diagnosed as having prostate cancer may not require therapy.[8] Results of the European Randomised Study of Screening for Prostate Cancer demonstrated a 20% mortality reduction attributable to screening and treatment; however, 48 additional men needed to be treated to prevent 1 prostate cancer death.[2] It is not currently possible to distinguish patients who require treatment to avoid

For editorial comment see p 2411.

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Table 1. Model Inputs for Disease-Related and Treatment-Related Probabilities

Annual Probabilities	Base-Case Estimate (SD)[a]	Range Used in Sensitivity Analysis
Disease-related probabilities		
Low-risk prostate cancer		
Biochemical recurrence after treatment[5-7]	Year 1, 0.01; lifetime risk, 0.45	Not varied
Progression from biochemical recurrence to metastatic disease[17]	0.05	Not varied
Death due to prostate cancer after development of metastatic disease[18]	0.22	Not varied
Active surveillance		
Progression to Gleason score ≥7[19]	0.0263 (0.007)	0.0132-0.526
Other progression (eg, PSA, DRE)[10,11,19]	0.0268 (0.007)	0.0134-0.536
Electing treatment	0.018 (0.005)	0.009-0.036
Development of metastatic disease prior to treatment	0.008	0.004-0.016
Intermediate-risk prostate cancer (Gleason score ≥7)		
Biochemical recurrence after treatment[20]	Year 1, 0.01; lifetime risk, 0.60	Not varied
Progression from biochemical recurrence to metastatic disease[17]	0.05	Not varied
Adverse effects of treatment		
Short term		
Radical prostatectomy[6]		
Perioperative death	0.0044 (0.00001)	0.0022-0.0088
Major complications[b]	0.0472 (0.0168)	0.0236-0.0944
Minor complications[c]	0.0948 (0.0019)	0.0474-0.1896
Urinary toxicity	0.47 (0.0578)	0.235-0.94
Erectile dysfunction	0.77 (0.0384)	0.385-1
Urethral stricture	0.0344 (0.002)	0.0172-0.0688
IMRT[5,7]		
Urinary toxicity[d]	0.3 (0.0835)	0.15-0.6
Gastrointestinal toxicity	0.18 (0.0506)	0.09-0.36
Brachytherapy[5,7]		
Urinary toxicity[d]	0.29 (0.058)	0.145-0.58
Acute urinary retention	0.1 (0.021)	0.05-0.2
Gastrointestinal toxicity	0.02 (0.001)	0.01-0.04
Active surveillance (biopsy)[21]		
Urosepsis	0.001 (0.0001)	0.0005-0.002
Acute urinary retention	0.026 (0.0049)	0.013-0.052
Long term		
Radical prostatectomy[6]		
Urinary toxicity	0.127 (0.011)	0.0635-0.254
Erectile dysfunction	0.453 (0.021)	0.2265-0.906
IMRT[5,7]		
Urinary toxicity[d]	0.04 (0.02)	0.02-0.08
Gastrointestinal toxicity	0.03 (0.01)	0.01-0.04
Erectile dysfunction	0.124 (0.028)	0.032-0.128
Secondary malignancy	0.0003 (0.00008); 1% lifetime risk beginning 10 y after treatment	0.00015-0.0006
Brachytherapy[5-7]		
Urinary toxicity[d]	0.06 (0.039)	0.025-0.10
Gastrointestinal toxicity	0.01 (0.008)	0.005-0.02
Erectile dysfunction	0.124 (0.028)	0.032-0.128
Secondary malignancy	0.00015 (0.000038); 0.5% lifetime risk beginning 10 y after treatment	0.000075-0.0003

(continued)

prostate cancer morbidity and mortality from those who will die with but not because of their cancer. Active surveillance is an alternative to initial treatment for men with low-risk, clinically localized disease that has the potential to mitigate overtreatment.

Active surveillance is a strategy of close monitoring for carefully selected patients with low-risk prostate cancer. The intent of active surveillance is to avert treatment unless disease progression occurs or a patient chooses treatment, in which case treatment with curative intent is undertaken. The results of several observational cohorts of active surveillance have been promising, but follow-up has been relatively short.[9-13]

We performed a decision analysis to assess the quality-adjusted life expectancy (QALE) of active surveillance compared with initial definitive treatment with radical prostatectomy, intensity-modulated radiation therapy (IMRT), or brachytherapy.

METHODS

We constructed a state transition model analyzed using Monte Carlo simulation with TreeAge Pro Suite 2009, version 1.0.2,[14] to estimate health benefits (QALE) accruing to men with low-risk, clinically localized prostate cancer (PSA <10 ng/mL, stage ≤T2a disease, and Gleason score ≤6).[15] In the model, men are treated at diagnosis or undergo active surveillance. Men enter the model at age 65 years and exit at time of death due to prostate cancer or another cause. The decision tree structure is shown in eFigure 1 (available online at http://www.jama.com).

Initial Treatment

Men in this cohort undergo treatment with IMRT, brachytherapy, or open retropubic nerve-sparing radical prostatectomy. Once treated, men are at risk of recurrence as evidenced by an increase in PSA (biochemical recurrence). If a man develops biochemical recurrence, he is at risk of progression to metastatic disease and death due to prostate cancer or another cause.

Table 2. Model Inputs for Utilities for Health States[a]

Health State	Utility (SD) [Range]
Prostate cancer	
Active surveillance[36]	0.83 (0.24) [0.42-1]
Biochemical recurrence	0.68 (0.26) [0.34-1]
Metastatic cancer	0.12 (0.18) [0.06-0.24]
Treatment of adverse effects	
Impotence	0.88 (0.20) [0.44-1]
Urinary difficulty	0.88 (0.16) [0.44-1]
Urinary incontinence	0.81 (0.30) [0.40-1]
Bowel problems	0.63 (0.32) [0.32-1]
Impotence and urinary difficulty	0.77 (0.24) [0.38-1]
Impotence and urinary incontinence	0.84 (0.23) [0.42-1]
Urinary incontinence and bowel problems	0.64 (0.33) [0.32-1]
Impotence and bowel problems	0.55 (0.35) [0.23-1]
Impotence, urinary incontinence, and bowel problems	0.38 (0.30) [0.19-0.75]
Major complications of radical prostatectomy[b]	0.96 (0.012) [0.48-1]
Minor complications of radical prostatectomy[c]	1
Other health states	
Posttreatment without adverse effects[36]	0.80 (0.24) [0.4-1]
Treatment with radical prostatectomy[d]	0.46 (0.36) [0.23-0.92]
Treatment with radiation therapy[d]	1 [0.5-1]

[a] Utilities are from Stewart et al[37] and unpublished data (Stewart et al; 2009) except as otherwise noted.
[b] Weighted average of disutilities of component complications (major bleeding, deep vein thrombosis/pulmonary embolism, systemic infection, myocardial infarction/cerebrovascular accident, bowel injury) from Sullivan and Ghushchyan.[38]
[c] Because minor surgical complications did not involve significant treatment, no decrement in utility was assigned to these complications.
[d] The treatment with radical prostatectomy utility reflected only the utility for undergoing radical prostatectomy without complications, erectile dysfunction, or urinary symptoms. No utility was found in the literature that reflected only the utility for undergoing radiation therapy without adverse effects; sensitivity analysis was performed on a wide range.

base case, utilities were elicited from men without a diagnosis of prostate cancer using the time–trade-off method, in which individuals are asked to define the amount of time they would be willing to sacrifice to be in a better health state vs a poorer health state (TABLE 2).[36-38] Sensitivity analyses were conducted using patient-derived utilities. In the model, patients maintain posttreatment utilities until death, with the exception of utilities related to short-term adverse effects and erectile dysfunction attributed to androgen deprivation therapy.

Sensitivity, Threshold, and Probabilistic Sensitivity Analyses

We conducted 1-way and multiway sensitivity analyses around key variables (ranges are given in Table 1 and Table 2). Threshold analyses were performed to identify probability and utility values at which the optimal strategy (as defined by the highest QALE) changed. Sensitivity analysis was also performed to assess the effect of discounting on model results (eTable 2).

Probabilistic sensitivity analysis was performed and effectiveness calculated for each strategy from 500 samples consisting of 100 000 individual trials run with unique sets of draws from independent distributions around 45 parameters, including probability of prostate cancer–specific death during active surveillance, complications and adverse effects of treatment, and utilities. Uncertainty around event probabilities and utilities was represented using β distributions (Table 1) except for uncertainty around the probability of developing metastatic disease prior to treatment during active surveillance, which was estimated using a uniform distribution.

RESULTS

Base Case

In men aged 65 years, active surveillance, with IMRT for progression, was the most effective strategy (defined as the strategy associated with the highest QALE) producing 11.02 QALYs. Brachytherapy and IMRT were less effective at 10.5 and 10.43 QALYs, respectively. Radical prostatectomy was the least effective treatment, yielding 10.23 QALYs. The difference between the most and least effective initial treatment was 0.25 QALYs, or 3 months of QALE. In contrast, active surveillance provided 6.2 additional months of QALE compared with brachytherapy, the most effective initial treatment.

In the base case, 61% of men initially followed up with active surveillance underwent definitive treatment during their lifetimes because of progressive disease or patient choice at a median of 8.5 years after diagnosis, similar to recent published experience.[9-11,13,39] The risk of prostate cancer–specific death was 9% for initial treatment and 11% for active surveillance in the model.

Active Surveillance: Evaluation of Key Model Parameters

The results of sensitivity and threshold analyses in which active surveillance yielded a lower QALE than an initial treatment are reported herein. Analyses using patient-derived utilities (eTable 3 and eTable 4) and which varied the probability of disease progression during active surveillance (eTable 5), developing symptoms of disease during active surveillance (eTable 5), adverse effects of treatment (eTable 6), and the utilities associated with symptoms during active surveillance (eTable 7) resulted in QALE estimates favoring active surveillance.

Risk of Prostate Cancer–Specific Death. We conducted a threshold analysis to identify how much greater the risk of prostate cancer–specific death would have to be under active surveillance compared with initial treatment for the 2 approaches to be associated with equal QALE. For QALE to be equal, 15% of men undergoing active surveillance would have to die of prostate cancer as opposed to 9% who received initial treatment, a lifetime relative risk of

death of 0.6 for initial treatment vs surveillance.

Analyses of Utilities. The utility or value assigned by individuals to a particular health state is of central importance in the analysis of QALE. Two utilities were key to determining the favored strategy in the base case: (1) the utility for undergoing active surveillance and being at risk of cancer progression (living under active surveillance) and (2) the utility for having been treated and being at risk of recurrence but not experiencing adverse effects of treatment (posttreatment without adverse effects) (eTable 7 and eTable 8).

FIGURE 1 demonstrates this dependence. The line on the graph represents the points at which the QALE of active surveillance was equal to initial treatment with brachytherapy; the shaded area to the right and below the line represents values of the utility for living under active surveillance at which active surveillance produced higher QALE than initial treatment. For example, if the utility for active surveillance was 0.83 (the base-case value), the posttreatment utility had to be less than 0.88 for active surveillance to remain associated with higher QALE. If the posttreatment utility was 0.8 (the base-case value), the utility for living under active surveillance had to be greater than 0.77 for active surveillance to be favored.

When deciding whether to undergo active surveillance, patients and clinicians must weigh the psychological burden of living with prostate cancer and the disease-specific risk of doing so. We therefore performed a threshold analysis simultaneously varying the utility for active surveillance and the incidence of prostate cancer–specific death to identify at which values of each active surveillance would continue to be favored over initial treatment. FIGURE 2 represents the values of utility for active surveillance and incidence of prostate cancer-specific death at which the QALE generated by the model is equal to initial treatment (with brachytherapy). For example, if the utility for active surveillance was 0.9, active surveillance produced a higher QALE than initial treatment even with a risk of prostate cancer–specific death of up to 19%.

Probabilistic Sensitivity Analysis. Given the considerable uncertainty surrounding the model inputs, we performed a probabilistic sensitivity analysis (TABLE 3). These results reflect the uncertainty surrounding each parameter in the model, including utilities, symptoms during active surveillance, adverse effects of treatment, and risk of prostate cancer–specific death during active surveillance. Although the confidence interval for each strategy is wide, the ranking of strategies and the magnitude of effect difference between the strategies was unaltered when uncertainty was incorporated. Moreover, there was no statistical advantage of any initial treatment over active surveillance.

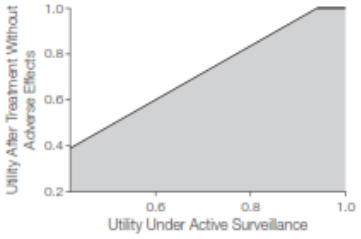
COMMENT

Men aged 65 years at diagnosis followed up with active surveillance received an additional 6.2 months of QALE compared with treatment with brachytherapy, the most effective initial treatment, in the base-case results. This analysis demonstrates that when a broad spectrum of possible disease- and quality of life–related outcomes associated with active surveillance and treatment is taken into account, active surveillance is a reasonable approach to consider in 65-year-old men with clinically localized, low-risk prostate cancer.

However, in the United States, active surveillance is used infrequently for management of prostate cancer. Although 16% to 40% of men newly diagnosed as having prostate cancer meet criteria for active surveillance, less than 10% of eligible men elect this approach.[40,41] Barriers to its use have included concerns about long-term disease outcomes, the perception that most men will ultimately undergo treatment, and concerns about the quality of life of men who elect active surveillance.[42,43]

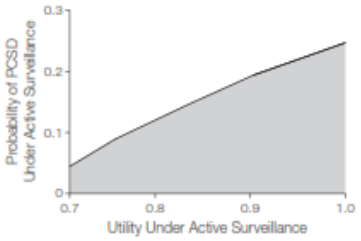
The long-term outcomes of men who undergo active surveillance are poorly characterized. Prospective studies of active surveillance have differing eligi-

Figure 1. Threshold Analysis of Utility for Living Under Active Surveillance and for Having Undergone Treatment Without Adverse Effects



Line indicates point at which quality-adjusted life expectancy of surveillance is equal to initial treatment. Shading indicates active surveillance favored over initial treatment.

Figure 2. Threshold Analysis of Utility for Being Under Active Surveillance and Probability of PCSD Under Active Surveillance



Line indicates point at which quality-adjusted life expectancy of active surveillance is equal to initial treatment. Shading indicates active surveillance favored over initial treatment. PCSD indicates prostate cancer–specific death.

Table 3. Probabilistic Sensitivity Analysis

Strategy	QALYs (95% Confidence Interval)	Incremental QALY
Active surveillance	11.02 (6.94-15.10)	
Brachytherapy	10.80 (5.37-16.23)	−0.22
IMRT	10.63 (5.42-15.89)	−0.17
Radical prostatectomy	10.41 (4.84-15.98)	−0.22

Abbreviations: IMRT, intensity-modulated radiation therapy; QALY, quality-adjusted life-year.

bility criteria and triggers for treatment, complicating the interpretation of results[9-11,13,39] (eTable 9). The relative merits of one set of eligibility criteria and treatment triggers over another for capturing clinically significant disease and minimizing overtreatment have not been established. Recently, Klotz et al[9] published results on the cohort with the longest median follow-up to date, 6.8 years. Thirty percent of the cohort progressed to definitive treatment; outcomes were favorable after short follow-up, with 97.2% 10-year prostate cancer–specific survival and 78.6% overall survival.

Given the uncertainty surrounding long-term outcomes with active surveillance, we analyzed the effect on the results of varying the estimates of prostate cancer–specific death and progressive disease during active surveillance. In the base case, we assumed that the relative risk of prostate cancer–specific death after initial treatment compared with active surveillance was 0.83, half that of radical prostatectomy compared with watchful waiting as reported in a randomized controlled trial.[24] In that trial, men were not screen-detected and in general had higher-risk disease than patients typically followed up with active surveillance, who are offered potentially curative treatment. The relative risk of prostate cancer–specific death was 0.65 (95% confidence interval, 0.45-0.94) for treatment vs watchful waiting in men of all ages; in men older than 65 years, the relative risk was 0.87 (95% confidence interval, 0.51-1.49) and was not significant. We chose 0.83 as the base case assumption of relative risk to approximate a conservative but reasonable risk of prostate cancer–specific death in the absence of a randomized controlled trial comparing treatment to active surveillance. We then performed sensitivity analyses to assess the point at which the QALE advantage of active surveillance could be overcome by a higher risk of prostate cancer–specific death. For active surveillance and initial treatment to be associated with equal QALE, the relative risk of prostate cancer–specific death after initial treatment vs active surveillance would have to be 0.6. Even if choosing active surveillance places men at a substantially higher risk of dying of prostate cancer or the risk of progressive disease on active surveillance is doubled, active surveillance is associated with higher QALE.

Few studies of quality of life in men undergoing active surveillance have been performed, and even fewer have measured utilities for active surveillance health states. However, anxiety in men who have chosen active surveillance or watchful waiting has not been shown to be higher than in men who elect initial treatment.[44-47]

In this analysis, active surveillance was favored over initial treatment for low-risk disease in men aged 65 years at diagnosis, but this result was highly dependent on the utility individuals place on living under active surveillance compared with having been treated.[48] In the base case, the utility for living under active surveillance was 0.83; having been treated without adverse effects of therapy but at risk of recurrence carried a utility of 0.80, 2 values taken from the same population.[36] If these values are varied, the results of the model change significantly. If the utility for active surveillance is raised above 0.94, active surveillance is favored no matter the utility assigned to the posttreatment health state. If the utility for the posttreatment health state is 0.80 (the base-case value), the utility for active surveillance must be greater than 0.77 for active surveillance to be favored. To place this utility in context, a utility of 0.77 is assigned to living with both impotence and urinary difficulty (Table 2). However, there is no posttreatment utility at which initial treatment is favored independent of the utility for living under active surveillance. Figure 1 demonstrates the importance of utilities in the model results but also reflects the central role of patient preference in the decision-making process.

These findings challenge the perception that active surveillance is a reasonable approach only if the risk of prostate cancer–specific death is equal to that seen with initial treatment. We found that as the utility for living under active surveillance increases, the minimal risk of prostate cancer–specific death associated with active surveillance necessary for initial treatment to be favored increases as well (Figure 2). This analysis simulates the decision-making process experienced by patients and physicians, who must weigh disease-specific and psychological risks of active surveillance.

Probabilistic sensitivity analysis indicates the degree to which uncertainty surrounding each variable affects the results as a whole. The uncertainty surrounding the probabilities and utilities used in the model reflects the gaps in the published literature from which we generated the model inputs. We have been conservative in modeling, assuming a high degree of uncertainty in the distribution parameters and no correlation between events, thereby exaggerating the uncertainty in the results. The overlapping confidence intervals seen in this analysis are therefore not unexpected. However, the ranking of strategies and the magnitude of benefit of active surveillance compared with other strategies mirror the base-case results. The contribution of the probabilistic sensitivity analysis, and of this analysis as a whole, lies in the finding that despite substantial uncertainty surrounding this clinical question, active surveillance appears to be a reasonable alternative to initial treatment.

To our knowledge, this is the first decision analysis comparing active surveillance with initial treatment for low-risk prostate cancer. Previous decision analyses have compared watchful waiting with initial treatment.[18,48-52] The most recent decision analysis[48] used probabilities derived from Bill-Axelson et al[53] for the watchful waiting cohort and found that, in contrast to our study, initial treatment was associated with a benefit in QALE for men with low- and medium-risk disease aged 70 years when average, patient-derived preferences were used. How-

ever, as in our study, individual patient preferences were critical in determining the optimal treatment for patients with low-risk disease.

This decision analysis modeled outcomes only for 65-year-old men; therefore, interpretation of these results must be limited to this population. Most studies performed to date in younger men have demonstrated disease-specific outcomes equivalent to older men.[54-58] However, given the uncertainty surrounding long-term outcomes in men followed up with active surveillance, presenting results including younger men would have required extensive sensitivity analysis and discussion surrounding this issue. In addition, this model does not incorporate comorbidities common in older men. Including analyses of younger or older men would have limited the ability to consider the importance of utilities in the outcomes in healthy 65-year-old men, the focus of this analysis.

Additional limitations of this study reflect those in the literature on which model inputs were based. The results of randomized studies comparing active surveillance with initial treatment are expected to emerge over the next few years. A more comprehensive catalog of prostate cancer health states is needed, as is an assessment of the disutility associated with uncertainty among men who choose not to be actively treated.[37] In addition, the use of adjuvant and salvage radiation therapy after radical prostatectomy was not modeled. In this low-risk population, the use of subsequent radiation therapy is relatively rare, and given the magnitude of QALE benefit of active surveillance compared with radical prostatectomy, it is unlikely that including a small survival benefit from subsequent radiation would substantively alter these conclusions.[59-62]

The quality-of-life advantage associated with active surveillance is robust in this model of treatment alternatives for men with clinically localized, low-risk prostate cancer. This benefit reflects the deferred and substantially lower incidence of adverse effects of treatment experienced by men under active surveillance. Active surveillance is associated with significant improvements in QALE even in analyses in which the probability of dying of prostate cancer or of developing progressive disease during active surveillance is increased. However, the finding that the optimal strategy is sensitive to utility weights is evidence that the decision whether to pursue active surveillance must be individualized. Models that incorporate individual patient utilities should be developed to assist patients and their caregivers to estimate the risks and potential benefits of active surveillance before making this decision.

Author Contributions: Dr Hayes had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Hayes, Ollendorf, Pearson, Barry, Stahl, McMahon.
Acquisition of data: Hayes, Ollendorf, Pearson, Stewart, Bhatnagar, McMahon.
Analysis and interpretation of data: Hayes, Ollendorf, Pearson, Barry, Kantoff, Stewart, Sweeney, Stahl, McMahon.
Drafting of the manuscript: Hayes, Ollendorf, Pearson, Barry, Sweeney, Stahl, McMahon.
Critical revision of the manuscript for important intellectual content: Ollendorf, Pearson, Barry, Kantoff, Stewart, Bhatnagar, Stahl, McMahon.
Statistical analysis: Hayes, Ollendorf, Pearson, McMahon.
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Annals of Internal Medicine | ORIGINAL RESEARCH

Observation Versus Initial Treatment for Men With Localized, Low-Risk Prostate Cancer

A Cost-Effectiveness Analysis

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Background: Observation is underutilized among men with localized, low-risk prostate cancer.

Objective: To assess the costs and benefits of observation versus initial treatment.

Design: Decision analysis simulating treatment or observation.

Data Sources: Medicare schedules, published literature.

Target Population: Men aged 65 and 75 years who had newly diagnosed low-risk prostate cancer (prostate-specific antigen level <10 μg/L, stage ≤T2a, Gleason score ≤3 + 3).

Time Horizon: Lifetime.

Perspective: Societal.

Intervention: Treatment (brachytherapy, intensity-modulated radiation therapy, or radical prostatectomy) or observation (active surveillance [AS] or watchful waiting [WW]).

Outcome Measures: Quality-adjusted life expectancy and costs.

Results of Base-Case Analysis: Observation was more effective and less costly than initial treatment. Compared with AS, WW provided 2 additional months of quality-adjusted life expectancy (9.02 vs. 8.85 years) at a savings of $15 374 ($24 520 vs. $39 894) in men aged 65 years and 2 additional months (6.14 vs. 5.98 years) at a savings of $11 746 ($18 302 vs. $30 048) in men aged 75 years. Brachytherapy was the most effective and least expensive initial treatment.

Results of Sensitivity Analysis: Treatment became more effective than observation when it led to more dramatic reductions in prostate cancer death (hazard ratio, 0.47 vs. WW and 0.64 vs. AS). Active surveillance became as effective as WW in men aged 65 years when the probability of progressing to treatment on AS decreased below 63% or when the quality of life with AS versus WW was 4% higher in men aged 65 years or 1% higher in men aged 75 years. Watchful waiting remained least expensive in all analyses.

Limitation: Results depend on outcomes reported in the published literature, which is limited.

Conclusion: Among these men, observation is more effective and costs less than initial treatment, and WW is most effective and least expensive under a wide range of clinical scenarios.

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The optimal management of men with low-risk, clinically localized prostate cancer is controversial. In the prostate-specific antigen (PSA) era, up to 70% of these men have low-risk disease (PSA level <10 μg/L, stage ≤T2a, Gleason score ≤3 + 3) and less than 6% risk for prostate cancer–specific death at 15 years (1–4). More than 90% of these men are treated with radical prostatectomy (RP), external beam radiation, or brachytherapy (BT) (5), but as many as 60% may not have required therapy in their lives (6). Most men who undergo treatment have at least 1 long-term adverse effect (7–9).

The cost of unnecessary treatment is not limited to adverse effects. In 2000, diagnosis and treatment was estimated to cost $1.3 billion in the United States, an increase of 30% since 1994 (10). A recent analysis estimated that the cost of diagnosis and treatment is slightly more than $5 million to prevent 1 prostate cancer death (11).

Observation is an alternative to treatment for men with localized, low-risk disease and takes the form of active surveillance (AS) and watchful waiting (WW). With AS, men are followed closely—typically with serial PSA tests, digital rectal examinations, and biopsies—and treated with curative intent if the disease progresses. In the most mature series, 30% of men were ultimately treated, and prostate cancer–specific survival was 97.2% at 10 years (12).

With WW, men are observed without monitoring and given palliative treatment when the disease becomes symptomatic. Traditionally, this approach has been reserved for men expected to die with, not of, prostate cancer, usually because of advanced age or comorbid conditions. However, in subgroup analyses of PIVOT (Prostate Cancer Intervention Versus Observation Trial), which followed 731 men (median age, 67 years) who had been randomly assigned to RP or WW for a median of 10 years (13), men with low-risk prostate cancer derived no benefit from RP compared with WW in all-cause mortality (hazard ratio [HR], 1.15 [95% CI, 0.80 to 1.66]) or prostate cancer–specific mortality (HR, 1.48 [CI, 0.42 to 5.24]). The

See also:

Web-Only
CME quiz
Supplements

Context

Most men with localized, low-risk prostate cancer are treated soon after diagnosis.

Contribution

This analysis used recent trial data to show that observation slightly improves quality-adjusted life expectancy and is less expensive than treatment after diagnosis for men aged 65 and 75 years with localized prostate cancer. Treatment would have to be markedly more effective than current data suggest for the conclusion to be overturned.

Caution

The model was based on many assumptions given the scarcity of data for outcomes with treatment and observation.

Implication

Compared with treatment after diagnosis, observation is cost-effective for men aged 65 to 75 years under a wide range of clinical scenarios.

—The Editors

PRoTECT (Prostate Testing for Cancer and Treatment) trial (14), comparing active monitoring, RP, and radiotherapy, will also yield useful information about the relative benefits of observation with monitoring but will not close enrollment until 2015.

We recently did a decision analysis suggesting that quality-adjusted life expectancy (QALE) improves with AS compared with initial treatment (15), and previous cost analyses have suggested that observation is less expensive than initial treatment (16, 17) but did not formally estimate cost-effectiveness. Therefore, we did a cost-effectiveness analysis of AS and WW compared with initial treatment of low-risk, clinically localized prostate cancer in men aged 65 and 75 years.

METHODS

We developed a state transition model using TreeAge Pro software (TreeAge Software, Williamstown, Massachusetts) and did a Monte Carlo simulation to estimate the costs and health benefits for men with low-risk, clinically localized prostate cancer treated with intensity-modulated radiation therapy (IMRT), BT, open RP (in men aged 65 years only; robotic prostatectomy was not modeled), AS, or WW (**Supplement 1**, available at www.annals.org). Health benefits were described in months or years of QALE (15). Costs were derived from Medicare reimbursements and average wages for age-matched men. Men were aged 65 or 75 years on model entry, and they exited at death. Costs and health benefits were discounted at 3% annually. We used a societal perspective, in accordance with the Panel on Cost-Effectiveness in Health and Medicine (18).

Treatment Strategies

The AS strategy comprised PSA tests every 3 months, digital rectal examinations every 6 months, and biopsies at 1 year and every 3 years thereafter (12). Men who progressed to more aggressive disease (Gleason histology score of 7 on repeated biopsy, clinical or biochemical progression) or selected treatment received IMRT; in the base case, BT and RP were not modeled in men treated with AS. Ten percent of men who developed a Gleason score of 7 had "unfavorable risk" disease and received 6 months of androgen-deprivation therapy with IMRT (19).

The WW strategy reproduced the PIVOT experience. Men were followed with visits and PSA tests every 6 months and bone scans every 5 years, and 20.4% of men were treated over 10 years (49% with RP, 39% with IMRT, and 12% with BT) (13).

Model Inputs

Model inputs were generated from a systematic review updated through June 2012 and from PIVOT; probabilities were estimated using random-effects meta-analysis (13, 15) (**Table 1**, **Appendix 1**, **Appendix Table 1**, and **Appendix Figure 1**, available at www.annals.org). The model was calibrated to ensure that its performance was consistent with assumptions. Internal validation was done to ensure that model outputs were consistent with model inputs; external validation demonstrated that model outputs were consistent with outcomes reported in the literature (**Appendix 1**).

All men treated initially were assumed to have the HR point estimate of 1.48 reported in PIVOT for prostate cancer–specific death compared with WW (13). We assumed as a base case that AS would provide 25% additional benefit compared with WW in preventing prostate cancer–specific death and used an HR for prostate cancer–specific death for treatment compared with AS of 1.85. We changed 2 probabilities from the previous decision analysis to reflect the publication of updated results of AS cohorts (12, 22, 23, 25–28): The annual probability of Gleason progression on AS decreased to 2.3% from 2.7%, and the annual probability of developing other signs of disease progression increased to 5.2% from 2.7% (**Table 1**) (15).

We classified adverse effects of treatment as short-term (occurring and resolving within 90 days) and long-term (occurring or persisting at least 90 days after treatment and persisting for life) (**Tables 1** to **3** and **Appendix Table 1**).

Utilities

Utilities for health states were elicited using a time-tradeoff method from men without prostate cancer (range, 0 [deceased] to 1 [perfect health]) (15). For men in more than 1 health state simultaneously (for example, on AS with urinary obstructive symptoms), we multiplied utilities (**Table 2** and **Appendix Table 1**).

Table 1. **Model Inputs for Key Probabilities***

Annual Disease-Related Probabilities	Base-Case Estimate (SD)†	Range Used in Sensitivity Analysis
Low-risk prostate cancer		
Biochemical recurrence after treatment (7–9)	0.01 (year 1; lifetime risk, 0.45)	Not varied
Progression from biochemical recurrence to metastatic disease (20)	0.05	Not varied
Death from prostate cancer after development of metastatic disease (21)	0.22	Not varied
AS		
Progressing to Gleason score of 7 (12, 22, 23, 24)	0.023 (0.006)	0.012–0.046
Other progression (PSA test, DRE) (12, 22, 23, 25–28)	0.052 (0.013)	0.026–0.104
Electing to have treatment	0.018 (0.005)	0.009–0.036
Development of metastatic disease before treatment	0.00003‡	Not varied
WW		
Progression to treatment (13)	0.02 (0.005)	0.01–0.04
Intermediate-risk prostate cancer (Gleason score ≥7)		
Biochemical recurrence after treatment (19)	0.01 (year 1; lifetime risk, 0.60)	Not varied
Progression from biochemical recurrence to metastatic disease (20)	0.05	Not varied

AS = active surveillance; DRE = digital rectal examination; PSA = prostate-specific antigen; WW = watchful waiting.
* For further details, see **Appendix Table 1** (available at www.annals.org).
† Where SDs are provided, the parameter was varied (range, 0–1) in probabilistic sensitivity analysis using a β-distribution function in TreeAge Pro parameterized with approximations of *a* and *b* (range, 0–1) based on the mean and SD using formulas in **Appendix Figure 1** (available at www.annals.org).
‡ Uniform distribution used in probabilistic sensitivity analysis.

Costs

We input costs in 2012 U.S. dollars for initial treatment of prostate cancer, ongoing treatment of erectile dysfunction and urinary obstructive symptoms existing before treatment, surveillance, treatment of short- and long-term adverse effects, and patient time costs (**Table 3**, **Appendix 1**, and **Supplement 2**, available at www.annals.org) (31). We included inpatient and outpatient direct and indirect medical costs derived from the Centers for Medicare & Medicaid Services Hospital Outpatient Prospective Payment System (32). We valued patient time at $165 per day, assuming an 8-hour workday at the 2012 U.S. median wage, for men 65 years or older (33).

Sensitivity, Alternative, and Threshold Analyses

We did 1-way sensitivity analyses on key parameters, including the PIVOT-based HRs for prostate cancer–specific death (13) (**Appendix Table 2**, available at www.annals.org); the probability of progressing to treatment on WW and AS (**Appendix Table 3**, available at www.annals.org); the probability of progressing to the PIVOT distribution of treatments (RP, IMRT, or BT) among men receiving AS (**Appendix Table 4**, available at www.annals.org); the utility of being on observation; and treatment, surveillance, and patient time costs and discounting rates (**Appendix Tables 5** to **9**, available at www.annals.org). In threshold analyses, we identified parameter values at which strategy rankings changed (**Table 4**). In probabilistic sensitivity analyses (those done simultaneously on all model parameters [probabilities, costs, and utilities] to quantify the cumulative effect of uncertainty on the results), we simulated 100 000 individuals for each of 500 samples drawn from independent distributions representing the uncertainty surrounding estimates of probabilities, utilities, and costs for each strategy (**Appendix 2**, **Appendix Figures 2** and **3**, and **Appendix Table 10**, available at www.annals.org).

Role of the Funding Source

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RESULTS

In this model comparing observation using WW or AS with initial treatment, the lifetime risk for death from

Table 2. **Model Inputs for Key Utilities***

Health State	Utility (SD)†	Range
Prostate cancer		
AS (15, 29)	0.83 (0.24)	0.42–1
WW (29)	0.83 (0.24)	0.42–1
Biochemical recurrence (29)	0.68 (0.26)	Not varied
Metastatic cancer (29)	0.12 (0.18)	Not varied
After treatment without side effects (30)	0.80 (0.24)	0.4–1

AS = active surveillance; WW = watchful waiting.
* For further details, see **Appendix Table 1** (available at www.annals.org).
† Where SDs are provided, the parameter was varied (range, 0–1) in probabilistic sensitivity analysis using a β-distribution function in TreeAge Pro parameterized with approximations of *a* and *b* (range, 0–1) based on the mean and SD using the formulas in **Appendix Figure 1** (available at www.annals.org).

Table 3. **Model Inputs for Key Costs***

Costs	Base-Case Estimate, $
Direct costs†	
Surveillance costs	
Physician visit with PSA test	140
Incremental cost of biopsy with prophylactic antibiotics	688
PSA test only	29
Bone scan	320
Procedure costs	
RP (open)	11 856
IMRT	23 817
BT	11 511
ADT	9090
Short-term adverse effects and complications	
Minor complications of RP	8259
Major complications of RP	19 687
Septicemia after biopsy	13 355
Urinary symptoms of treatment	221
Acute urinary retention (BT)	210
Bowel symptoms of treatment	1306
Urethral stricture (RP)	587
Long-term adverse effects and symptoms	
Incontinence (including 1-time costs)	698
Incontinence (recurrent costs)	503
Bowel effects (including 1-time costs)	1557
Bowel effects (recurrent costs)	26
Erectile dysfunction (including 1-time costs)	393
Erectile dysfunction (recurrent costs)	154
Underlying urinary obstruction	968
Underlying erectile dysfunction	366
Patient time costs	
Daily patient wage	165
Surveillance costs	
PSA test or provider visits	83
Visit with TRUS-guided biopsy	165
Bone scan	83
Procedure costs	
RP (open)	445
BT	825
IMRT	1857
ADT	165
Short-term adverse effects and complications	
Minor complications of RP	592
Major complications of RP	1564
Septicemia after biopsy	938
Urinary symptoms	115
Acute urinary retention (BT)	152
Bowel symptoms	1975
Urethral stricture (RP)	165
Long-term adverse effects and symptoms	
Incontinence (including 1-time costs)	386
Incontinence (recurrent costs)	83
Bowel effects (including 1-time costs)	2434
Bowel effects (recurrent costs)	140
Erectile dysfunction (including 1-time costs)	182
Erectile dysfunction (recurrent costs)	83
Underlying urinary obstruction	667
Underlying erectile dysfunction	83

ADT = androgen-deprivation therapy; BT = brachytherapy; IMRT = intensity-modulated radiation therapy; PSA = prostate-specific antigen; RP = radical prostatectomy; TRUS = transrectal ultrasonography.
* For further details, see **Appendix Table 1** (available at www.annals.org).
† For sources of costs, see the Methods section and **Appendix 1** (available at www.annals.org).

prostate cancer was 4.8% for men on AS, 6.0% for men on WW, and 8.9% for men treated initially (**Table 5**). Life expectancy was similar among the strategies: 81.6 years for men on AS, 81.4 years for men on WW, and 81.2 years for men treated initially. Among men aged 65 years, 78% on AS were treated over their lifetimes compared with 34% on WW, at a median of 6.8 and 12.4 years after diagnosis, respectively. Among men aged 75 years, 61% on AS and 23% on WW were treated a median of 5.4 and 8.4 years after diagnosis, respectively.

Among all strategies in men aged 65 years, WW offered the most QALE at the lowest cost (**Table 5**) and was cost-saving compared with AS, providing 2 additional months of QALE for $15 374 less. Both observational strategies were more effective than initial treatment, but AS was more expensive than BT (by $4520) and RP (by $1714). Brachytherapy was the most effective therapy at 8.14 years of QALE but cost an additional $10 854 compared with WW. Intensity-modulated radiation therapy was similar to BT in effect but, at $48 699, was the most expensive strategy. Quality-adjusted life expectancy was poorest with RP (7.95 years).

Estimates were qualitatively similar in men aged 75 years. Watchful waiting was most effective and least expensive, providing 6.08 years of QALE at a cost of $18 302. Active surveillance provided 2 fewer months of QALE but cost an additional $11 746 compared with WW. Brachytherapy was again the most effective and least expensive initial treatment (less expensive than AS by $1238). Intensity-modulated radiation therapy was the least effective and most expensive strategy.

For all but WW, the largest cost was treatment of prostate cancer (including the average cost of the procedure and patient time costs) (**Appendix Table 11**, available at www.annals.org). For men aged 65 years, RP was least expensive ($12 199) and IMRT was most expensive ($25 569). The cost of treatment for men in the AS cohort overall (with IMRT) was $15 688. On WW, the greatest costs were associated with treating underlying erectile dysfunction and urinary symptoms. The cost of surveillance of men diagnosed with prostate cancer (before and after treatment) was highest in those on AS for men aged 65 and 75 years.

Sensitivity Analysis of Disease-Related Parameters

When we changed the HR for prostate cancer–specific death to the lower confidence bound of the PIVOT point estimate for the comparison of treatment and observation, the scenario least favorable to observation, both WW and AS became less effective than any initial treatment in men aged 65 years; WW remained least expensive (**Appendix Table 2**). The HR for prostate cancer–specific death at which the QALE with observation was equal to the most effective treatment, BT, was 0.47 for WW and 0.64 for AS, meaning that treatment would have to be 53% better

than WW and 36% better than AS to overcome the QALE advantage of observation.

Results were qualitatively similar in men aged 75 years. Watchful waiting was less effective than AS under the base case (5.76 vs. 5.98 years of QALE) when the HR for prostate cancer–specific death for treatment compared with WW was reduced to the lower confidence bound, but it remained less expensive. Active surveillance was less effective than WW with the same change (5.57 v. 5.76 years of QALE), and the rankings of costs did not change. The HR for prostate cancer–specific death at which QALE on WW was equal to initial treatment was 0.31 in men aged 75 years; for AS, it was 0.42.

When the HR for prostate cancer–specific death for treatment versus AS was doubled from baseline (HR for treatment of 3.7 relative to AS), AS remained less effective than WW and the ranking of costs did not change (**Appendix Table 2**). The HR for prostate cancer–specific death for treatment versus AS would have to be 7.71 in men aged 65 years and 4.3 in men aged 75 years for AS to be equal to WW (**Table 4**).

Active surveillance became favored over WW if the probability of having treatment on AS decreased below 63% in men aged 65 years and 42% in men aged 75 years (**Table 4** and **Appendix Table 3**). If the probability of having treatment on AS or WW doubled, the rankings did not change. In an analysis in which men having AS progressed to a distribution of RP, IMRT, and BT identical to that in PIVOT, the QALE did not change substantially. Active surveillance remained more expensive than WW by $10 500 in men aged 65 years and $7900 in men aged 75 years, but it became less expensive than BT by $289 in men aged 65 years and $2633 in men aged 75 years.

Table 4. **Threshold Analyses of Scenarios in Which the QALE of AS Is Equal to or Better Than That of WW***

Model Parameter	AS Base Case	Threshold Value at Which AS QALE Is Equal to or Better Than WW QALE
Men aged 65 y		
HR for prostate cancer–specific death for treatment vs. AS	1.85	≥7.71
Lifetime probability of being treated on AS, %	78	≤63
Utility of AS at which AS is favored over WW	0.83	≥0.87
Men aged 75 y		
HR for prostate cancer–specific death for treatment vs. AS	1.85	≥4.30
Lifetime probability of being treated on AS, %	61	≤42
Utility of AS at which AS is favored over WW	0.83	≥0.84

AS = active surveillance; HR = hazard ratio; QALE = quality-adjusted life expectancy; WW = watchful waiting.
* WW remains less expensive than AS under every reasonable scenario modeled.

Sensitivity Analysis of Utility of Being on Observation

In men aged 65 years, the QALE of AS and WW became equal when the utility of being on AS increased from 0.83 to 0.87. In men aged 75 years, the QALE of AS and WW became equal when the utility of being on observation increased from 0.83 to 0.84 (**Table 4**).

Sensitivity Analyses of Costs

In all analyses varying costs, WW remained least expensive (**Appendix Tables 5** to **8**). For AS to be equal to WW in cost, we had to set the cost of treatment equal to that of BT, the least expensive treatment; reduce costs of surveillance and treating short- and long-term adverse effects of treatment by 50%; and decrease the probability of being treated by 40%.

Probabilistic Sensitivity Analysis

The ranking of strategies and magnitude of effect difference between strategies was unaltered in probabilistic sensitivity analyses that incorporated uncertainty in esti-

Table 5. **Base-Case Average Lifetime Costs and QALE for Men Aged 65 and 75 Years**

Strategy	Cost, $	Incremental Cost, $	QALE, y	Incremental QALE, y	Men Treated, %	Died of Prostate Cancer, %
Men aged 65 y						
WW	24 520	–	9.02	–	34	6.0
BT	35 374	10 854	8.14	−0.88	100	8.9
RP	38 180	13 660	7.95	−1.07	100	8.9
AS	39 894	15 374	8.85	−0.17	78	4.8
IMRT	48 699	24 179	8.10	−0.92	100	8.9
Men aged 75 y*						
WW	18 302	–	6.14	–	23	2.6
BT	28 810	10 508	5.56	−0.58	100	3.9
AS	30 048	11 746	5.98	−0.16	61	2.1
IMRT	42 286	23 984	5.52	−0.62	100	3.9

AS = active surveillance; BT = brachytherapy; IMRT = intensity-modulated radiation therapy; QALE = quality-adjusted life expectancy; RP = radical prostatectomy; WW = watchful waiting.
* RP not modeled in men aged 75 y.

mates for men aged 65 and 75 years (**Appendix Figures 2** and **3** and **Appendix Table 10**). However, overlapping CIs surrounding both costs and QALE reflect the collective uncertainty surrounding all of the model inputs (**Appendix 2**).

DISCUSSION

Mounting evidence suggests that many men with localized, low-risk prostate cancer are treated unnecessarily at substantial personal and societal cost. In this study, we demonstrated that both WW and AS are associated with improved QALE compared with initial treatment and that WW is cost-saving compared with any other strategy in men aged 65 and 75 years at diagnosis. Watchful waiting was more effective than AS or initial treatment in all but 3 scenarios modeled (**Table 4**) and remained less expensive in every 1-way sensitivity analysis conducted.

The QALE advantage of WW was lost if treatment became associated with substantial improvements in prostate cancer–specific death. Because of variability in patient selection, surveillance protocols, and the dearth of data in the WW literature after PSA screening, we based our WW simulation on PIVOT (13, 34), the first randomized trial comparing observation with initial treatment in a screened population. In the base case, we assumed that the HR for prostate cancer–specific death for treatment versus WW was the point estimate reported in the low-risk subset of PIVOT. No trials have compared AS with WW: Given its emphasis on intervention and curative treatment, we assumed that AS would perform 25% better in preventing prostate cancer–specific death than WW and then varied this HR over a wide range. For treatment to yield a higher QALE, it would have to provide a survival benefit at least 50% better than WW and 36% better than AS.

The QALE advantage of WW was also lost when we varied the probability of progression to treatment with AS. In the absence of long-term follow-up of studies of observation, we assumed constant rates of conversion from observation to treatment. Active surveillance became favored over WW if the probability of progressing to treatment on AS decreased by more than 15% in men aged 65 years and more than 19% in men aged 75 years.

Active surveillance also yielded a higher QALE than WW when the utility of being on AS was increased. As previously reported, utilities are key to the QALE advantage associated with AS versus initial treatment (15). In the base case, we assumed no difference in utility between AS and WW in the absence of literature values. Sensitivity analyses found that increasing the utility on AS from 0.83 to 0.87 in men aged 65 years or to 0.84 in men aged 75 years made AS equivalent to WW.

Watchful waiting remained the least expensive in all but the most extreme scenario modeled as a result of the magnitude of difference in cost in the number of men treated, treating adverse effects of treatment, and surveillance. The high cost of AS was primarily due to the cost of curative treatment and surveillance. In the base case, men on AS who convert to treatment receive IMRT, the most expensive method. Active surveillance remained substantially more expensive than WW in the sensitivity analysis in which the same treatment distribution was used for AS as for WW, although its cost was slightly less than that of initial treatment with BT.

In a recent decision analysis, Keegan and colleagues (17) compared the costs of AS with initial treatment with RP, radiation therapy, BT, and primary androgen-deprivation therapy. Active surveillance was associated with a per-patient cost savings of $16 042 (CI, $16 039 to $16 046) after 5 years and $9944 (CI, $9941 to $9948) after 10 years of follow-up (17). This study used hospital costs at a single institution, and costs were lower because it did not incorporate the costs of symptoms on AS or the costs of treatment of adverse effects, in contrast to our study. Corcoran and colleagues (35) compared a combination of WW and AS with RP and found that RP was more expensive, at $15 235 versus $6558 to $11 992 for WW and AS (depending on the rate of conversion to RP and surveillance schedule). However, this analysis used a 15-year time horizon and an annual conversion rate between 5% and 7%. Our annual rate of conversion to treatment of 9% in the base case of AS reflects the more current data used in our analysis, and our lifetime horizon results in higher costs for AS and WW in our study. One recent analysis has modeled the prostate cancer–specific mortality rate of AS compared with AS followed by RP and found that RP was associated with 1.8 months of additional life expectancy (36), but no studies to date have done cost-effectiveness analyses for WW and AS compared with initial treatment.

The limitations of our study reflect, in part, limitations of the literature. We used point estimates from a subgroup analysis in PIVOT, a study criticized for being underpowered. Although the estimate of the HR for prostate cancer–specific death for treatment versus AS is a reasonable assumption, no data exist to compare AS with WW or with treatment, although we calibrated our model to PIVOT and validated it using the published literature (**Appendix 1**). We assumed a constant rate of conversion from observation to treatment, but it may diminish with time. The rates of progression to treatment in our model are similar to those reported in the literature (34% in men aged 75 years and 37% in men aged 65 years after 5 years) (12, 22, 23, 25–28), but to date, most Gleason score upgrading on biopsy has occurred within several years of diagnosis (37–39). In the absence of data in the literature, men who progressed on AS received IMRT in our base case because most men are eligible for this treatment in contrast to BT or RP, for which eligibility is limited by prostate volume and comorbid conditions, respectively, thus biasing results against AS in terms of cost. Utilities are central to any analysis of QALE, and the lack of a stan-

dardized catalog of prostate cancer health states is a hindrance to modeling cost-effectiveness in this disease. We have attempted to address all of these concerns in sensitivity and probabilistic sensitivity analyses. We have not included a cost-effectiveness acceptability curve to illustrate uncertainty surrounding the willingness-to-pay threshold. However, given the debate surrounding the existence of an accepted threshold in this country, we believe that the probabilistic sensitivity analysis conveys the uncertainty and magnitude of our results in a transparent way (40). Despite the considerable uncertainty surrounding inputs in this model and the limitations of this study, one may conclude that observation is a reasonable and, in some situations, cost-saving alternative to initial treatment.

In this analysis, observation was associated with improved QALE compared with initial treatment in men with low-risk prostate cancer. Watchful waiting provided greater QALE benefit compared with initial treatment than AS, but this finding was dependent on several model assumptions. As has been demonstrated, preferences are central to the QALE advantage of observation, and the decision about which strategy to pursue must be an individual one. Using our results, we estimated that if the number of newly diagnosed men with low-risk prostate cancer who selected observation with WW increased from 10% to 50%, it would result in a cost savings of more than $1 billion; if one half of the men who chose observation opted for WW and one half for AS, it would save $500 million. As we better classify men as low risk by adding molecular and imaging techniques currently in development to standard clinical parameters, prospective studies should determine whether less surveillance than is typically done on AS is safe for men who select observation for low-risk prostate cancer. These findings provide further support for WW and AS as reasonable and underutilized options for men with low-risk prostate cancer.

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